IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo, et al.

SERIAL NO.: 09/918,127

FILED: July 30, 2001

FOR: Pharmaceutical Compositions of Cholesteryl Ester Transfer Protein Inhibitors

Examiner: Fubara, Blessing M.
Art Unit: 1615

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.131

I, Douglas A. Lorenz, declare that:

1. This declaration is to establish completion of the invention of this application in the United States at a date prior to February 10, 1999, that is the effective date of U.S. Patent 6,706,283 that was cited by the examiner.

2. I am one of the inventors of the instant application.

3. To establish the date of completion of the invention of this application, reproductions of notebook entries are submitted as evidence as Exhibits A and B.

4. From these documents it can be seen that the invention in this application was made in the United States at least by the date of February 9, 1999, which is a date earlier than the effective date of the reference.

5. In particular attached to this declaration are notebook pages related to work I performed and supervised in connection with the process used to form solid amorphous dispersions of a cholesteryl ester transfer protein (CETP) inhibitor. The notebook pages attached as Exhibit A show that a CETP inhibitor was spray dried with the polymers hydroxypropylmethyl cellulose acetate succinate (HPMCAS), hydroxypropylmethyl cellulose phthalate (HPMCP), hydroxypropylmethyl cellulose (HPMC), polyvinylpyrrolidone (PVP), cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT) to form a solid amorphous dispersion. The notebook pages attached as Exhibit B show that the solid amorphous dispersion particles were dissolution tested and showed concentration-enhancement relative to the crystalline drug alone. This work was performed prior to February 9, 1999.

DECLARATION

6. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Douglas A. Lorenz

Date: 10-13-04

NOTEBOOK NO. 1659
ISSUED TO Doug Lorenz
ON _____ 19____
DEPARTMENT _____
RETURNED _____ 19____

—SCIENTIFIC NOTEBOOK CO.—
2831 LAWRENCE AVE.
P.O. BOX 238
STEVENSVILLE, MI 49127
616-429-8285

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TEMPLATE FOR EXPERIMENTAL WORK

Graphs/Sketches
Estimate Trends of Key Experiment(s)

Overall Hypothesis
Physical Model of Technology or Problem

Determine the feasibility of using high energy forms of CP-529,414 to increase the solubility + bioavailability of the drug.

Specific Study Goals
What is the key question about the hypothesis these experiments will answer?

What CP-529,414: polymer HPD's have best dissolution performance during initial screening?

Experimental
Key Experimental Conditions — mini spray dryer

T = 100°C/30°C, P = 30 psig, Flow = 30 gauge reading, Rate = 1.3 mL/min

Results/Conclusions
Key Results: Did we strengthen or weaken the hypothesis?

Spray went OK — See performance + potency data on later pages.

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Project No.

TITLE Book No. 119

From Page No.

CP-529414 HEDs - (1659-119)

1659-119a
3.0 mg CP-529414 (#N36721-145-2)
27 mg HPMCAS-LF (302022)
10 g acetone

1659-119b
27 mg HPMCAS-MF (203002)
3.0 mg CP-529414
10 g acetone

1659-119c
3.0 mg CP-529414
27 mg HPMCAS-HF (312060)
10 g acetone

1659-119d
3.0 mg CP-529414
27 mg HPMCP (408343)
10g acetone

1659-119e
3.0 mg CP-529414
27 mg HPMC (E3 Prem - MM92071021E)
10 g acetone/MeOH 1/1

1659-119f
3.0 mg CP-529414
27 mg PVP K-29/32 (Tx40430C)
10 g acetone/MeOH 9/1

1659-119g
3.0 mg CP-529414
27 mg CAP (60616)
10 g acetone

1659-119h
3.0 mg CP-529414
27 mg CAT (21201)
10 g acetone

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TEMPLATE FOR EXPERIMENTAL WORK

Graphs/Sketches
Estimate Trends of Key Experiment(s)

Overall Hypothesis
Physical Model of Technology or Problem

Determine the feasibility of using high energy forms of CP-529,414 to increase the solubility and bioavailability of the drug.

Specific Study Goals
What is the key question about the hypothesis these experiments will answer?

What is the PBS dissolution performance (initial screening) of 10% CP-529,414 : polymer HEDs + what HED(s) give best performance?

Experimental
Key Experimental Conditions

Dissolved @ night w/ additional experimental detail outlined in 1454-139 HRN 2B.

Results/Conclusions
Key Results: Did we strengthen or weaken the hypothesis?

CAP, CAT + MF HEDs appear to be most promising in PBS receptor solution.

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TITLE

Book No.

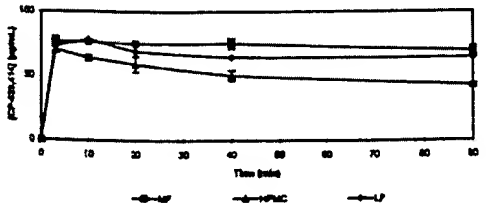
From Page No.

10% CP-529,414 polymer HEDs — Performance initial screening — PBS receptor solution — Theor Cmax = 100ug/mL — See disso results attached below + results/ conclusions @ left —

Title	Dissolution Performance of 10% CP-529,414 HEDs With Various Polymers in PBS
Drug	1.8 mg CP-529,414:HPMCAS-LF 10%HED (BRI Ref. No. 1654-137) 1.8 mg CP-529,414:HPMCAS-MF 10%HED (BRI Ref. No. 1654-119B) 1.8 mg CP-529,414:HPMC 10%HED (BRI Ref. No. 1654-119E)
Receptor Solution	1.8 mL PBS, pH 6.5, 290 mOsm
Date Performed	Redacted Notebook 1654-139
Operator	HRN
Objective	Determine dissolution performance of 10% CP-529,414 HEDs made with HPMCAS-LF, HPMCAS-MF, and HPMC in PBS.
Methods	Micro Centrifuge Method. Drug potency and dissolution performance measured by HPLC.
Comments	All work performed in a 37°C temperature controlled box.

Results

Sample	C_{max} (µg/mL)	AUC_{90} (min*µg/mL)	$C_{t=90}$ (µg/mL)	Theor C_{max} (µg/mL)
LF	76	5,900	17	87
MF	77	6,500	51	102
HPMC	70	4,800	18	111



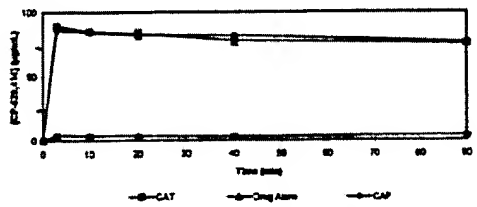
Conclusions: HEDs made with LF and MF have the good dissolution performance. However, HEDs made with CAP and CAT have better dissolution performance.

Plans

Title	Dissolution Performance of 10% CP-529,414 HEDs With Various Polymers and Drug Alone in PBS
Drug	1.8 mg CP-529,414:CAP 10%HED (BRI Ref. No. 1659-119D) 1.8 mg CP-529,414 CAT 10%HED (BRI Ref. No. 1659-119H) 0.18 mg CP-529,414 (Lot No. 36721-145-2)
Receptor Solution	1.8 mL PBS, pH 6.5, 290 mOsm
Date Performed	Redacted Notebook 1654-139
Operator	HRN
Objective	Determine dissolution performance of 10% CP-529,414 HEDs made with CAP and CAT in PBS. Compare to dissolution performance of drug alone in PBS.
Methods	Micro Centrifuge Method. Drug potency and dissolution performance measured by HPLC.
Comments	All work performed in a 37°C temperature controlled box.

Results

Sample	C_{max} (µg/mL)	AUC_{90} (min*µg/mL)	$C_{t=90}$ (µg/mL)	Theor C_{max} (µg/mL)
CAP	84	7,100	32	99
CAT	89	7,000	28	103
Drug Alone	4	300	2	100



Conclusions: HEDs made with CAP and CAT have very similar dissolution profiles and perform much better than drug alone.

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NOTEBOOK NO. 1654

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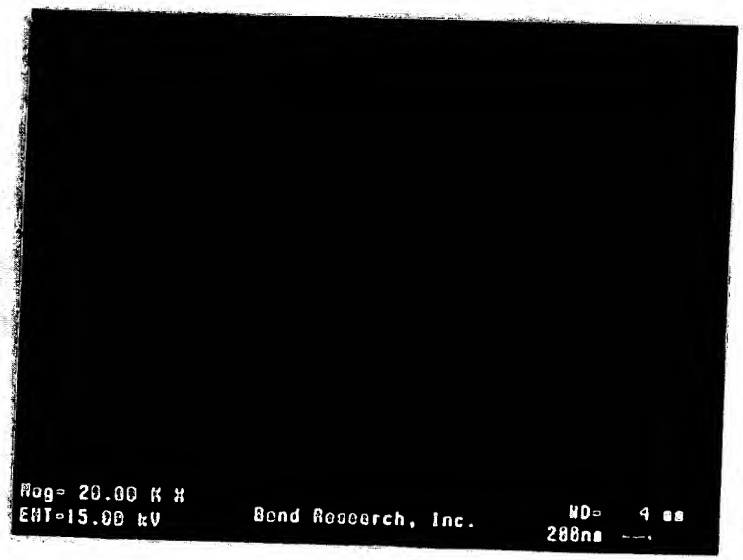

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1 Probe = 25 pA

138 **TEMPLATE FOR EXPERIMENTAL WORK**

Graphs/Sketches

Estimate Trends of Key Experiment(s)

Overall Hypothesis

Physical Model of Technology or Problem

Specific Study Goa

What is the key questior

Title	**Dissolution Performance of 10% CP-529,414 HEDs With Various Polymers and Drug Alone In PBS**
Drug	1.8 mg CP-529,414:CAP 10%HED (BRI Ref. No. 1659-119G) 1.8 mg CP-529,414:CAT 10%HED (BRI Ref. No. 1659-119H) 0.18 mg CP-529,414 (Lot No. 36721-145-2)
Receptor Solution	1.8 mL PBS, pH 6.5, 290 mOsm
Date Performed	Redacted **Notebook** 1654-139
Operator	HRN
Objective	Determine dissolution performance of 10% CP-529,414 HEDs made with CAP and CAT in PBS. Compare to dissolution performance of drug alone in PBS.
Methods	Micro Centrifuge Method. Drug potency and dissolution performance measured by HPLC.
Comments	All work performed in a 37°C temperature controlled box.

Results

Sample	C_{max} (µg/mL)	AUC_{60} (min*µg/mL)	C_{1250} (µg/mL)	Theor C_{max} (µg/mL)
CAP	86	7,100	32	99
CAT	89	7,000	26	103
Drug Alone	4	300	2	100

Experimental

Key Experimental Condi

Standard
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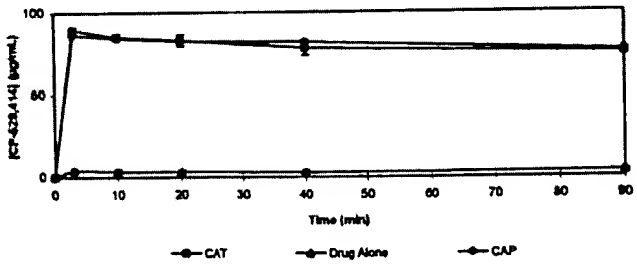

MF DSon

Conclusions HEDs made with CAP and CAT have very similar dissolution profiles and perform much better than drug alone.

Plans

Results/Conclusion

Key Results: Did we stre

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f Key Experiment(s)

Overall Hypothes
Physical Model of Tec

Specific Study Goals
What is the key question a

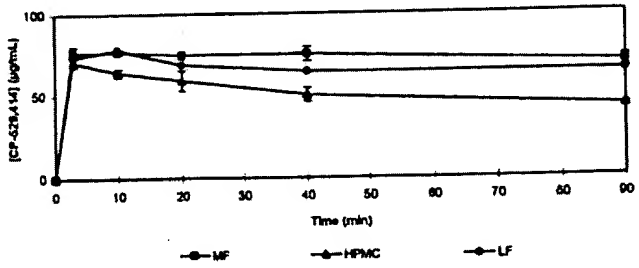
Title	**Dissolution Performance of 10% CP-529,414 HEDs With Various Polymers In PBS**
Drug	1.8 mg CP-529,414:HPMCAS-LF 10%HED (BRI Ref. No. 1654-137) 1.8 mg CP-529,414:HPMCAS-MF 10%HED (BRI Ref. No. 1654-119B) 1.8 mg CP-529,414:HPMC 10%HED (BRI Ref. No. 1654-119E)
Receptor Solution	1.8 mL PBS, pH 6.5, 290 mOsm
Date Performed	Redacted **Notebook** 1654-139
Operator	HRN
Objective	Determine dissolution performance of 10% CP-529,414 HEDs made with HPMCAS-LF, HPMCAS-MF, and HPMC in PBS.
Methods	Micro Centrifuge Method. Drug potency and dissolution performance measured by HPLC.
Comments	All work performed in a 37°C temperature controlled box.

Experimental
Key Experimental Conditi

Standard method

Results

Sample	C_{max} (µg/mL)	AUC_{90} (min*µg/mL)	C_{1200} (µg/mL)	Theor C_{max} (µg/mL)
LF	78	5,900	17	87
MF	77	6,500	51	102
HPMC	70	4,600	18	111



MF DSon

Results/Conclusions
Key Results: Did we stre

Conclusions HEDs made with LF and MF have the good dissolution performance. However, HEDs made with CAP and CAT have better dissolution performance.

Plans

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Key Experiment(s)

Overall Hypothes

Physical Model of Tecl

Specific Study Goals

What is the key question about the hypothesis these experiments will answer?

Experimental

Key Experimental Conditions

standard micro centrifuge dilns - PBS instead of MFDS on
method P. 16 of this book

Results/Conclusions

Key Results: Did we strengthen or weaken the hypothesis?

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TITLE Diso CR529414 PBS Book No. 1654

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PBS
1 a+b 1.80 mg 10% CR529414 : LF (1654-137)
2 a+b " " : MF (1659-119B)
3 a+b " " : HPMC (1659-119E)
4 a+b " " : CAP (1659-119G)
5 a+b " " : CAT (1659-119H)
6 a+b 0.18 mg CR529414 (Lot # 36721-145-2)

MFDS 7 a+b 1.80 mg 10% CR529414 : LF (1654-137)

1 LF 1654-137 90 MFDS 7
2 MF 1659-119b
3 HPMC 1659-119c
4 CAP 119g
5 CAT 119h
6 drug alone 36721-145-2

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